BIOGRAPHICAL SKETCH

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NAME: Martinez Zamudio, Ricardo

eRA COMMONS USER NAME (credential, e.g., agency login): zamudiori

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
Royal Holloway University of London, Egham, Surrey	BS	08/2006	Biochemistry (biotechnology)
Georgetown University, Washington, DC	PHD	07/2012	Biochemistry & Molecular Biology
Pasteur Institut, Paris, Ile-de-France	Postdoctoral Fellow	02/2017	Genomics & Epigenetics
Rutgers University, Newark, New Jersey	Postdoctoral Fellow	10/2022	Genomics & Epigenetics

A. Personal Statement

I have recently started my position as an independent investigator at Rutgers-Robert Wood Johnson Medical School, Department of Pharmacology, where I am establishing a research program on the function of transcription factor (TF) networks during cell fate transitions in the early stages of cancer development as well as in aging of the immune system. My previous scientific training took place in competitive and multidisciplinary laboratories in Mexico, the UK, the USA and France, funded by predoctoral and postdoctoral fellowships I have won. My research focuses on the chromatin-based regulation of transcription by integrating multiomic, cell isolation and computational approaches and has resulted in important contributions to the field of epigenetics. These contributions include: i) the discovery of a novel histone ADP-ribosylation-dependent chromatin remodeling mechanism which facilitates inflammatory gene expression by disrupting nucleosome structure, ii) the identification and manipulation of the oncogene-induced senescence (OIS) transcription factor (TF) network as well as the development of senescence-associated gene signatures with prognostic potential for the outcome of anticancer therapy and iii) the development of a method for the identification and isolation of live senescent cells from human tissues, which we recently applied to identify and characterize the senescent CD8+ T cell population in human peripheral blood. Overall, my scientific contributions findings provide the foundation for my research program as an independent investigator and highlight the value of integrating high-throughput sequencing, cell isolation and computational approaches as a successful strategy to manipulate cell fates and obtain prognostic information.

Recently completed projects and support during my postdoctoral stage include:

NIH-supported projects:

R01 CA136533 (PI: Utz Herbig) 2/1/2017-1/31/2022
NIH/NCI
Deciphering the Code For Senescence Escape During Cancer progression in Humans
Major goals: Understand the chromatin-based mechanisms driving senescence escape in human tumors.
Role: Postdoctoral Scientist

R21 AG067368 (PI: Utz Herbig and Patricia Fitzgerald-Bocarsly) 5/1/20-4/30/2022
NIH/NIA
Causes of Immune Cell Senescence in Aging Humans

Major Goals: 1) Identify and characterize senescent immune cells in humans, 2) identify the underlying causes of immune cell senescence and 3) define the contribution of senescent cells to disease.
Role: Postdoctoral Scientist

International agency-supported projects:

Four-dimensional chromatin changes during cellular senescence and senescence bypass
Major goals: Define and manipulate the epigenetic mechanisms driving cells into the senescent state.
Role: Fellow/Principal Investigator

Supporting agencies:

La Ligue Nationale Contre le Cancer Postdoctoral Fellowship (France)	2/2014-2/2017
Mexican National Scientific Council Postdoctoral Fellowship (Mexico)	2/2014-2/2016

Citations:

1. **Martínez-Zamudio R.I.**, Stefa A, Nabuco J, Vasilopoulos T, Simpson M, Doré G, Roux P, Galan M, Chokshi R, Bischof O, Herbig U. Escape From Oncogene-Induced Senescence is Controlled by POU2F2 and Memorized by Chromatin Scars. [preprint]. 2022 July. doi: 10.1101/2022.06.29.497942. Under review at Cell Genomics.
2. **Martínez-Zamudio R.I.**, Dewald H, Vasilopoulos T, Gittens-Williams L, Fitzgerald-Bocarsly P, Herbig U. Senescence-associated β-galactosidase reveals the abundance of senescent CD8+ T cells in aging humans. Aging Cell. 2021 May; 20(5):-. doi: 10.1111/acel.13344.
3. **Martínez-Zamudio R.I.**, Roux P, de Freitas J, Robinson L, Doré G, Sun B, Belenki D, Milanovic M, Herbig U, Schmitt C, Gil J, Bischof O. Author Correction: AP-1 imprints a reversible transcriptional programme of senescent cells. Nature Cell Biology (Journal Cover Article). 2020 September; 22(10):1286-1288. doi: 10.1038/s41556-020-00589-3.
4. **Martinez-Zamudio R.I.**, Ha H. Histone ADP-Ribosylation Facilitates Gene Transcription by Directly Remodeling Nucleosomes. Molecular and Cellular Biology. 2012 July; 32(13):2490-2502. doi: 10.1128/MCB.06667-11.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

Present	Assistant Professor, Rutgers-Robert Wood Johnson Medical School, Department of Pharmacology, Piscataway, NJ
2017 - 2022	Postdoctoral Fellow, Rutgers University, Center for Cell Signaling and Department of Microbiology, Biochemistry & Molecular Genetics, Newark, NJ
2014 - 2017	Postdoctoral fellow, Pasteur Institute, Department of Cell Biology and Infection, Paris
2006 – 2012	Doctoral Candidate, Georgetown University, Department of Biochemistry & Molecular Biology, Washingon, DC
2020-Present	Member. New Jersey Alliance for Clinical and Translational Science Society of Scholars
2017-Present	Member: International Cell Senescence Association

Honors

2022	Rutgers Presidential Faculty Scholar
2021	Rutgers University Nominee for the Regional Blavatnik Young Scientists Award
2019 - 2022	Mexican National Investigator System Level I, Mexican National Scientific Council
2016 - 2018	Mexican National Investigator System Level I, Mexican National Scientific Council
2006	GlaxoSmithKline award to the excellence in a biotechnology degree, Royal Holloway University of London

C. Contribution to Science

1. My doctoral research focused on elucidating the role of Poly(ADP)ribose Polymerase 1 (PARP1) enzymatic activity in facilitating inflammatory gene expression, resulting in two publications. I found that stimulation of macrophages and microglia with lipopolysaccharide (LPS) induced the enzymatic activity of PARP1 through the MAPK signaling pathway in the absence of DNA damage. PARP1 then ADP-ribosylates itself and nucleosomal histones, leading to the local relaxation of chromatin structure to allow the binding of NF-κB to the promoters of inflammatory genes, enhancing their expression. The most important contribution of this work is the discovery of an NAD^+-dependent chromatin remodeling mechanism involving the covalent ADP-ribosylation of nucleosomal histones, leading to the disruption of the nucleosome and increasing accessibility of DNA.

a. **Martinez-Zamudio R.I.** and Ha, H.C., (2014). *PARP1 enhances inflammatory cytokine expression by alteration of promoter chromatin structure in microglia*. Brain and Behavior 4(4):552-65. DOI: https://doi.org/10.1002/brb3.239
b. **Martinez-Zamudio R.I.** and Ha, H.C., (2012). *Histone ADP-Ribosylation Facilitates Gene Transcription by Directly Remodeling Nucleosomes.* Molecular and Cellular Biology 32(13):2490-2502. DOI: https://doi.org/10.1128/MCB.06667-11

2. At the Institut Pasteur, I was lead scientist on a project that focused on the identification and manipulation of the gene-regulatory networks driving cellular senescence. To achieve this, we used a time-resolved strategy involving the integration of epigenome, chromatin accessibility and transcriptional profiles during the transition to senescence in several human primary cell culture models. This strategy allowed us to identify an AP1-regulated transcription factor network that is instrumental in mediating the senescence transcriptional program. Importantly, we found that disruption of AP1 function reverses the senescence transcriptome to an earlier transitional stage in cultured cells and prevents senescence-associated gene expression upon chemotherapeutic treatment in a mouse model of B cell lymphoma. Furthermore, we revealed that an AP1-regulated senescence transcriptional signature discriminates treatment-responsive from treatment-resistant B cell lymphomas in both mice and humans. The manuscript related to this project, on which I am first author, was the cover article for the July 2020 issue of Nature Cell Biology. In relation to this project, we also published Cell Snapshot infographics, in which I am also first author.

a. **Martínez-Zamudio R.I.,** Roux P.F., et al (2020). *AP-1 Imprints a Reversible Transcriptional Programme of Senescent Cells*. Nature Cell Biology 22(7):842-855. ***Journal Cover Article.*** DOI: https://doi.org/10.1038/s41556-020-0529-5
b. **Martínez-Zamudio R.I.**, Robinson L, Roux P.F., Bischof O., (2017). *SnapShot: Cellular Senescence in Pathophysiology*. Cell 170(5):1044-1044. DOI: https://doi.org/10.1016/j.cell.2017.08.025
d. **Martínez-Zamudio R.I.**, Robinson L., Roux P.F., Bischof O., (2017). *SnapShot: Cellular Senescence Pathways.* Cell 170(4):816-816. DOI: https://doi.org/10.1016/j.cell.2017.07.049

3. My postdoctoral work at Rutgers University involved two main projects: i) developing methods to isolate and characterize live senescent cells from human tissues including tumors and blood, and ii) understanding the epigenomic mechanisms driving senescence escape and how this process relates to colon cancer progression. Regarding the first project, I developed an accurate and efficient method to isolate and characterize live senescent cells from human tissues. Using this method, we have provided the first accurate description and characterization of cellular senescence in human CD8+ T lymphocytes. We show that i) senescent CD8+ cells are abundant in aged humans, ii) CD8+ T cells develop senescence at any differentiation stage and iii) provide the first transcriptome of a pure population of naturally occurring senescent cells in humans. The manuscript related to this project was published in Aging Cell. With respect to the second project, by generating and integrating time-resolved multiomic profiles of human fibroblasts overexpressing oncogenic H-RAS V12, we revealed the mechanisms driving escape from OIS. Escape from OIS comprised organized waves of transcription factor (TF) activity at enhancers, defining two cell fate transitions: i) an OIS transition established by an AP1-dependent senescence enhancer landscape, and ii) an OIS escape transition defined by senescence enhancer remodeling and increased activity of POU/Homeobox TFs. Cells that escaped the OIS state carried over an epigenetic memory of OIS, which we refer to as 'senescence-associated chromatin scars (SACS)' and required the activity of the POU2F2 TF to re-enter the cell cycle. To provide biological relevance to our findings, we identified SACS- and POU2F2-associated gene signatures using public gene expression, chromatin

accessibility and clinical datasets of human colorectal cancer (CRC) and evaluated their prognostic potential in predicting relapse after surgery. We found that a SACS gene signature was predictive of no relapse after surgery while a POU2F2 gene signature was predictive of relapse after surgery in an analysis of 982 CRC samples. Collectively, our findings highlight the potential of dynamic multiomic profiling in identifying key regulators of senescence-associated cell fate transitions in cancer development and senescence-associated gene signatures with prognostic power. The manuscript related to this project is currently under review at Cell Genomics. In addition, I, along with my supervisor Dr. Utz Herbig, have published a review chapter in the upcoming Encyclopedia of Gerontology and Population Aging titled 'Cell Senescence'.

a. **Martínez-Zamudio R.I.**, Stefa A., et al, (2022). *Escape From Oncogene-Induced Senescence is Controlled by POU2F2 and Memorized by Chromatin Scars*. bioRxiv. DOI: https://doi.org/10.1101/2022.06.29.497942 (under review at Cell Genomics).
b. **Martínez-Zamudio R.I.**, Dewald H.K., et al (2021). *Senescence-associated β-galactosidase reveals the abundance of senescent CD8+ T cells in aging humans*. Aging Cell 20(5):e13344. DOI: https://doi.org/10.1111/acel.13344
c. **Martínez-Zamudio RI**, Herbig U., (2020). *Cell Senescence.* Encyclopedia of Gerontology and Population Aging (in press).